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Homophthalic Acid and Some of Its Derivatives

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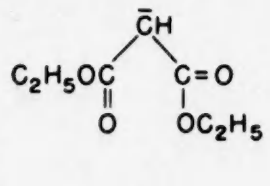
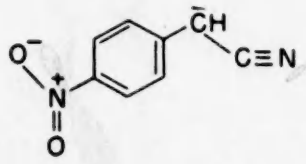
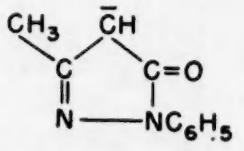
The term "active hydrogen compounds" covers acetylenes, enols and related compounds, and phenols. The difference between acetylenes and the other classes is distinct, but the difference between enols and phenols is one of degree rather than kind. A nonacetylenic, nonphenolic, active hydrogen compound (generalized *enol*) comprises a methylene or methine group bounded by two electron-attracting substituents, so that a central hydrogen atom becomes mobile and its carbon subject to attack by electron-seeking agents. Familiar examples are diethyl malonate (I), *p*-nitrophenylacetonitrile (II), and 1-phenyl-3-methyl-5-pyrazolone (III), all stabilized by resonance.



I

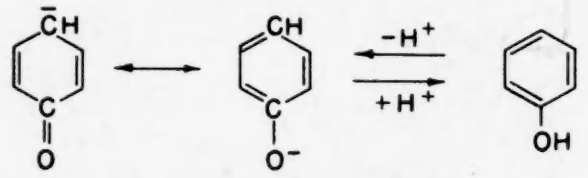


II



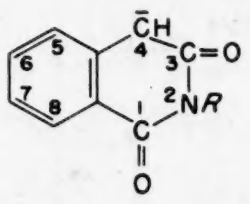
III

It is apparent from Formula II that the electron-attracting function may be extended by the principle of vinylogy. A *phenol* (IV) has such an extension, in a six-membered carbocyclic ring so constituted that *one* electron-attracting group fulfills the definitive function to *both* sides of the methylene group. Even though the form without unshared electrons on carbon is stabilized by aromatic resonance, phenols undergo the characteristic coupling reactions of active methylene compounds.



IV

If it is true that phenols and enols differ only in degree, there should be some sort of intermediate case. N-Substituted homophthalimide (isoquinoline-1,3-dione) (V) preserves the six-membered ring and the vinylogous 4-position activation of the phenols, but provides direct 2-position activation as well, with a heterocyclic insertion to prevent activation of the 3-position.



V

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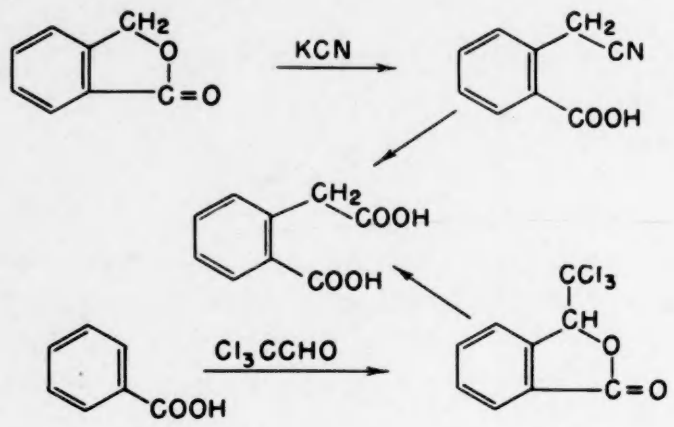
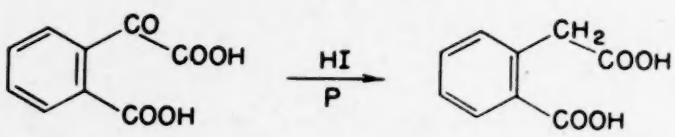
The methods of obtaining such compounds are well documented but have not hitherto been reviewed. The usual preliminary is the synthesis of a simple or substituted homophthalic acid.

Methods of Making Homophthalic Acids

A. *From phthalide* (1, 2, 3, 4, 5)

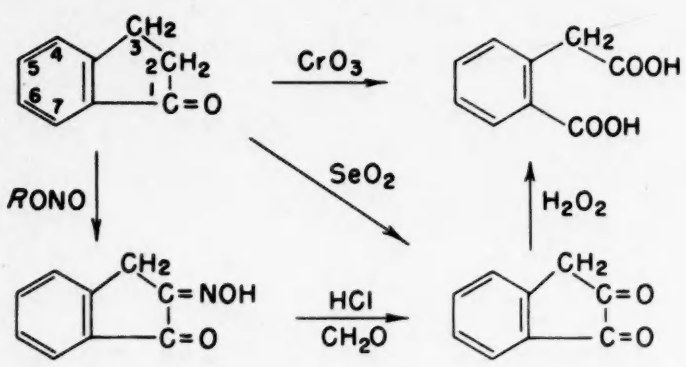


B. *Reduction of phthalonic acid* (6)

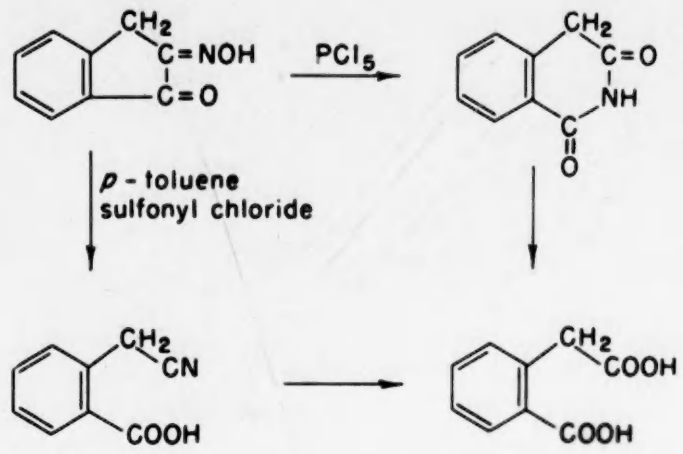


C. *Nitration and subsequent substitution of phthalide or homophthalic acid* (7, 1, 8)

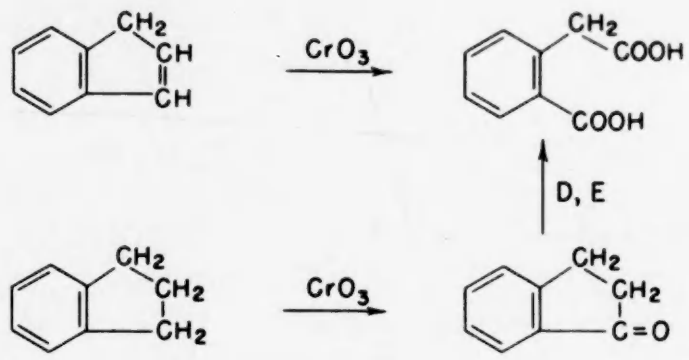
D. *Oxidation of indanones* (7, 9, 10, 11, 12)



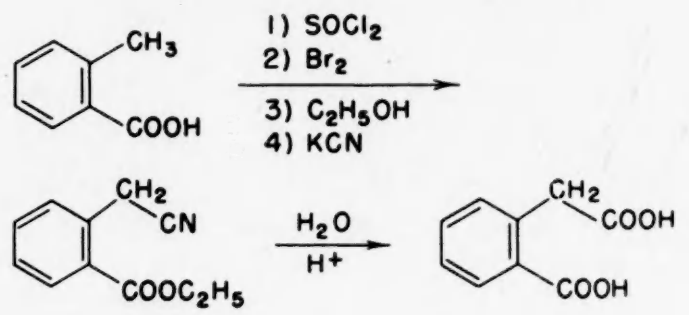
E. *Beckmann rearrangement* (13, 14, 15, 16)



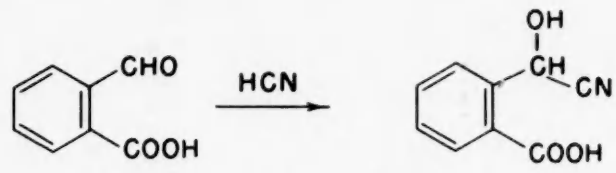
F. *Oxidation of indene and indane* (17, 18, 19)



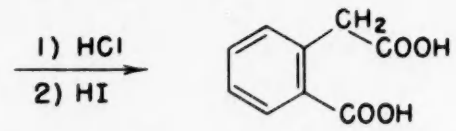
G. *Bromination of toluic acid* (20)



H. *From phthalaldehydic acid cyanohydrin* (5)



delta-lactones; cf. "A."



I. *Willgerodt reaction* (21)

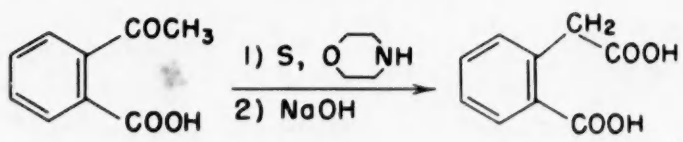
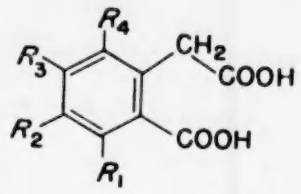


TABLE I: Some Known Homophthalic Acids



Substituent is hydrogen unless otherwise specified

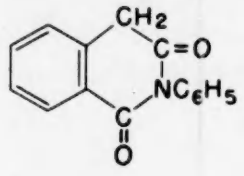
R_1	R_2	R_3	R_4	METHOD	REFERENCES
				A	2
				B	6
				D	9, 11
			CH_3	E	16
				F	8, 17, 18
				G	20
				I	21
CH_3O	CH_3O			E	14
CH_3O	CH_3O			H	5
HO		HO		J	22
	CH_3O	CH_3		A	4
	CH_3O			C	8
	CH_3O			E	15
	CH_3O	CH_3O		D	12
	CH_3O	CH_3O		E	13
	HO	HO	HO	A	3
	CH_3O	CH_3O	CH_3O	A	3
		CH_3O		C	7
		CH_3O		E	7
		CH_3O	CH_3O	E	15
	CH_3		HO	K	23
		CH_3	HO	A	4
	O_2N			C, D	7
	O_2N			C	1, 8
	H_2N			C	17

J. *Decarboxylation*—not general (22)

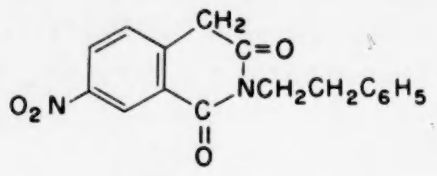
K. *Diels-Alder reaction*—not general (23)

The most flexible of these methods are "D" and "E." Hence, there is appended to the table (I) of known homophthalic acids a table (II) of compounds useful in these applications. For easy comparison, a uniform substituent numbering system is adopted.

In the cases which have been studied, water may be eliminated with the production of a homophthalic anhydride by boiling, under reflux, the appropriate acid and acetic anhydride or acetyl chloride (Refs. 17, 18, 34). Homophthalimides are produced from the mixture of a homophthalic acid or, better, a homophthalic anhydride, with a wide variety of amines, with or without an inert solvent, at 150-200° (VI, VII, Refs. 34, 35) or in boiling acetic acid (VIII, Ref. 17).

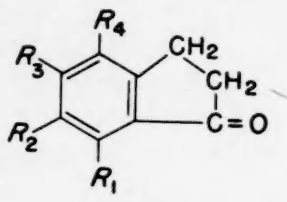


VI



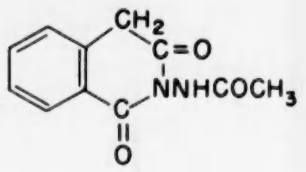
VII

TABLE II: Some Known Indanones for Methods "D" and "E" (and Indanes for Method "F")



Substituent is hydrogen unless otherwise specified

R_1	R_2	R_3	R_4	REMARKS	REFERENCE
HO				(Indane, 24)	25, 24, 19
CH_3O					26
CH_3O			CH_3		27
	CH_3O				7, 28
$(CH_3)_2CH$	CH_3O		CH_3		29
	C_2H_5O	CH_3O			30
		HO		(Indane, 31)	25, 31
		CH_3O			19, 32
CH_3			CH_3O		29
Benzo					33
	CH_3O	Benzo		(and dione)	10
	Tetramethylene				29
	O_2N				7
			O_2N		7



VIII

To settle the question of whether these homophthalimides may be considered intermediate between enols and phenols, recourse can be made to the coupling test mentioned on page 1. Acyclic and five-membered cyclic active hydrogen compounds couple in alkaline solution with *p*-nitrosodialkylanilines or oxidized *p*-aminodialkylanilines to form azomethine dyes ranging in color from yellow to blue (Ref. 36), that is, with absorption maxima at wave lengths of, roughly, 300 to 600 millimicrons. Phenols couple with the same reagents to form indophenols ranging from blue to green (Ref. 36); absorption maxima may be, in general, described as over 600 mμ.

The known N-substituted homophthalimides, under the same conditions, couple to form dyes that are, without exception, bright blue (Refs. 34, 35), with absorption maxima close to 600 mμ (Ref. 35).

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Determination of Carbohydrates and Carbohydrate Compounds Using Anthrone

Anthrone is used as a specific reagent for carbohydrates, both qualitatively and quantitatively. It gives a positive blue-green color reaction with all pure mono-, di-, and polysaccharides so far tested and reported. This reagent also gives a positive reaction with dextrins, dextrans, starches, plant polysaccharides, gums, pneumococcus polysaccharides of Types II and III, all glucosides tested, acetates of mono-, di-, and polysaccharides, and the hydrochlorides and sulfates of mannosidostreptomycin and dihydromannosidostreptomycin.

Furfural is the only non-carbohydrate which has been reported to give this reaction, the color of which changes rapidly to brown, and changes more rapidly upon dilution with sulfuric acid (1). The mannose compounds of streptomycin can be determined in commercial streptomycin.

Preparation of the reagent (2): Two grams of anthrone are added to a cooled mixture of one liter of concentrated sulfuric acid and 50 milliliters of distilled water.

Caution: The reagent should be freshly prepared every few days and all equipment and materials must be absolutely free of carbohydrate substances.

Procedure for carbohydrates (2): Five milliliters of the carbohydrate solution are measured into a 50-ml. beaker, and 10 milliliters of anthrone reagent are added and immediately mixed by swirling. After 10 minutes or more, the color is measured in an electrophotometer against a blank containing the reagent and distilled water. If a visual colorimeter is used, a comparison tube is prepared from standard glucose at the same time as the sample is prepared.

Using a color filter of 620 millimicrons (red), the color of the sample varies with Beer's law. A filter of 540 millimicrons (green) can be used but is not as sensitive.

Calculation of results will depend upon the type of instrument used.

Procedure for determining mannosidostreptomycin and dihydromannosidostreptomycin in commercial streptomycin (3): Enough commercial streptomycin is taken to give a concentration of mannosidostreptomycin or dihydromannosidostreptomycin equal to at least 5 micrograms of mannose per milliliter. The anthrone reagent is standardized with a known amount of mannose and the analytical procedure given is followed.

The conversion factor, K, for the mannose standards is calculated from the equation,

$$K = \frac{C \text{ (mannose concn.)}}{D \text{ (density of absorption)}}.$$

From this factor the mannose content of the streptomycin sample is calculated and then from this is calculated the content of mannosidostreptomycin or dihydromannosidostreptomycin. Mannosidostreptomycin hydrochloride contains 21.14 percent mannose; and the corresponding sulfate, 20.28 percent mannose.

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